Egyptian Journal of Anaesthesia (2014) **30**, 339–345

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
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Research Article

Efficacy of different dexmedetomidine regimens in producing controlled hypotensive anesthesia during functional endoscopic sinus surgery

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Received 19 December 2013; revised 25 March 2014; accepted 2 April 2014
Available online 13 May 2014

KEYWORDS

Dexmedetomidine;
Hypotensive anesthesia;
Alpha adrenergic agonists;
Nitroglycerin

Abstract *Background:* The study was designed to assess the ability of dexmedetomidine in different regimens to produce controlled hypotensive anesthesia during functional endoscopic sinus surgery in adults and the need to add an additional hypotensive agent in the form of nitroglycerin to achieve the target MAP.

Methods: In this blinded randomized controlled trail, 45 Patients, aged from 18 to 50 years, ASA physical status I and II, underwent endoscopic sinus surgery were enrolled in the study. Before induction of GA, all patients received bolus dexmedetomidine 1 μ/kg iv more than 10 min. After induction, Patients were randomly allocated into three groups, group Dex-0.4, in which patients received dexmedetomidine infusion as 0.4 μg/kg/h, group Dex-0.8, in which patients received dexmedetomidine infusion as 0.8 μg/kg/h and group Dex-P, in which patients received saline infusion. The target MAP was 55–65 mmHg, if not achieved by the infused study drug, nitroglycerin infusion was added in a titrating manner started with 0.1 μg/kg/min and increased gradually till the target MAP is reached. The surgical field quality was assessed by using Fromme et al. bleeding score.

Results: The intraoperative MAP in group Dex-P and group Dex-0.8 was maintained within target range at all time intervals. In group Dex-0.4, the MAP showed fluctuation to fall below and increased above the target range at different time intervals. Unlike the other two groups, no nitroglycerin infusion was needed in group Dex-0.8. Fromme et al. bleeding score showed the lowest values in Dex-0.8 group and the highest values in group Dex-0.4. The differences between the three groups were statistically significant with ($P < 0.05$).

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

 http://dx.doi.org/10.1016/j.egja.2014.04.001

Conclusion: Dexmedetomidine as bolus 1 μg/kg iv followed by iv infusion of 0.8 μg/kg/h or dexmedetomidine as pre-induction bolus 1 μg/kg iv followed by nitroglycerine iv infusion significantly decreased the mean arterial blood pressure to target values and provide satisfactory field quality.

1. Introduction

Functional endoscopic sinus surgery (FESS) is a minimally invasive procedure and is commonly performed under controlled hypotensive anesthesia [1].

Several pharmaceuticals have been used successfully to produce controlled hypotension during general anesthesia, for example inhalational anesthetics, direct vasodilators (sodium nitroprusside and nitroglycerin), beta adrenergic antagonists (propranolol and esmolol), alpha adrenergic agonists (clonidine and dexmedetomidine), calcium channel blockers, prostaglandin E1 (alprostadil) and adenosine [2] and μ-receptors agonists (remifentanil) [3,4].

Dexmedetomidine is a highly selective α2 adreno-receptor agonist with higher affinity to α2 adreno-receptor than clonidine, and this makes dexmedetomidine primarily sedative and anxiolytic [5]. The elimination half-life of dexmedetomidine ($t_{1/2\beta}$) is 2 h and the redistribution half-life ($T_{1/2\alpha}$) is 6 min, and this short half-life makes it an ideal drug for intravenous titration [6,7].

Several studies proved that intraoperative infusion of dexmedetomidine reduces the perioperative analgesic requirements [8,9], and others studies concluded that dexmedetomidine helps in reducing intraoperative blood pressure and provide satisfactory surgical field conditions [10–12].

The objectives of this prospective randomized controlled trial were to assess the efficacy of dexmedetomidine in different regimens to produce controlled hypotensive anesthesia during functional endoscopic sinus surgery in adults and the need to add an additional hypotensive agent in the form of nitroglycerin to achieve the target MAP. The primary outcome is the intraoperative MAP and the amount needed from an additional hypotensive agent nitroglycerin to achieve the targeted MAP. The secondary outcomes include intraoperative heart rate (HR), consumption of other vasoactive drugs (ephedrine, atropine), intra-operative surgical field quality, duration of recovery, postoperative sedation score and postoperative complications as hemodynamic instability, vomiting, desaturation or bleeding from surgical field.

2. Methodology

This study has been conducted in the of the Department of Anesthesia, ENT operating theater, Cairo University Hospitals through the period from June 2012 to June 2013 after being approved by the Departmental Research and Ethical Committee, and after obtaining informed consents from all patients. 45 Patients, aged from 18 to 50 years, ASA physical status I and II, underwent functional endoscopic sinus surgery were enrolled in the study. Patients with cardiovascular disease (hypertension, congestive heart failure, and coronary artery disease), cerebrovascular insufficiency, coagulation defects, history of renal or hepatic insufficiency, and hypersensitivity to the study drugs were excluded from the study.

On arrival to operating room, no sedation was given, iv line was cited and lactated ringer solution was infused 4–6 ml/kg/h. All patients were monitored with non-invasive blood pressure (BP), electrocardiograph ECG, pulse oximeter (SpO2) before induction of general anesthesia (GA), capnography for end-tidal CO2 ($_{ET}$CO2), radial artery cannula for intra-arterial blood pressure monitoring, and peripheral nerve stimulator (PNS) applied on the ulnar nerve for neuromuscular blockade after induction of GA. All patients received 1μ/kg iv dexmedetomidine bolus dose more than 10 min before induction of GA, then anesthesia was induced with propofol 2 mg/kg iv, fentanyl 1 μg/kg iv and atracurium besylate 0.5 mg/kg iv, when TOF count showed disappearance of T_1 (0/4), endotracheal intubation with appropriate size oral endotracheal tube was accomplished and lungs were mechanically ventilated to maintain the $_{ET}$CO2 30–35 mmHg. Anesthesia was maintained with inspired isoflurane 1.5 vol% and atracurium besylate top up doses 0.1 mg/kg/20–30 min was given guided with TOF count aiming to keep it as 1/4. Airway was secured by oro-pharyngeal packing and patients were positioned supine with head up 30°. Dexamethasone 0.2 mg/kg and metoclopramide 10 mg slowly iv were given as emesis prophylaxis.

Patients then were randomly allocated into three groups, group Dex-0.4, in which the patients received dexmedetomidine 0.4 μg/kg/h as continuous iv infusion at rate of 0.2 ml/kg/h from a prepared dexmedetomidine diluted in saline to a concentration of 2 μg/ml, group Dex-0.8 in which the patients received dexmedetomidine 0.8 μg/kg/h as continuous iv infusion at rate of 0.2 ml/kg/h from a prepared dexmedetomidine diluted in saline to a concentration of 4 μg/ml and group Dex-P (placebo) in which the patients received continuous iv infusion of 0.2 ml/kg/h of normal saline. The continuous iv infusion was maintained all through the procedure and terminated 10 min before termination of surgery and discontinuation of inhaled anesthetics. The syringes of the continuous infusion were prepared by an anesthesiologist who was not involved in data recording and infused through injector pumps with unidentified reservoirs to assure that the observing anesthesiologist remained blinded to the infused drug. The target MAP was 55–65 mmHg, if not achieved by the infused study drug, nitroglycerin infusion was added in a titrating manner started with 0.1 μg/kg/min and increased gradually till the target MAP is reached. If the MAP dropped below 55 mmHg, nitroglycerin infusion was decreased gradually till stopped and if the MAP is still below 55 mmHg, ephedrine 6 mg iv was given and could be repeated after 3 min. Atropine 0.01 mg/kg was given if HR decreased to 50 beat/min.

All patients were operated upon by the same surgeon. Bleeding in the surgical field and the quality of the visibility were assessed subjectively by the surgeon who was blinded to

the infused drug using 6 points scale by Fromm et al. scale [13] adapted by Boezaart et al. [15]: **0** = no bleeding, **1** = slight bleeding so blood evacuation not necessary, **2**: slight bleeding so sometimes blood has to be evacuated, **3** = low bleeding so blood has to be often evacuated and operative field is visible for some seconds after evacuation, **4** = average bleeding so blood has to be often evacuated, and operative field is visible only right after evacuation and **5** = high bleeding so constant blood evacuation is needed, sometimes bleeding exceeds evacuation and surgery is hardly possible. The 1st assessment was 30 min after the beginning of surgery and then every 30 min till the end of surgery.

All through the intraoperative period, mean arterial blood pressure (MAP), heart rate (HR), were recorded before starting the bolus infusion of dexmedetomidine (baseline), one minute after termination of the bolus dexmedetomidine, one minute after induction of GA, one minute after endotracheal intubation and then every 10 min throughout the surgery till patient recovery and one minute before transfer to the post-anesthesia care unit (PACU). The total amount of nitroglycerine consumed throughout the procedure was recorded for each patient as mg/patient. With termination of surgery, isoflurane was discontinued, the oropharyngeal pack was removed and the oropharynx was suctioned under direct vision using the rigid laryngoscope. The residual atracurium was reversed with neostigmine 0.05 μ/kg iv and atropine 0.02 mg/kg iv when the TOF count is 2/4, trachea was extubated once the patients showed eye opening and purposeful movement and then patients were transferred to PACU where BP, SpO2 and ECG were monitored. O2 supplementation was provided via face mask. Sedation was assessed using Ramsay sedation score (Appendix-1) on arrival to PACU, and then every 30 min for 2 h. Complications such as desaturation due to bronchospasm, laryngospasm, bleeding from surgical site or vomiting were recorded and managed. Recovery characteristics were measured using Modified Aldrete's Score (MAS) on arrival to the PACU and every 30 min. Patients were discharged from the PACU after achieving a modified Aldrete's score of $\geqslant 9$. The duration of surgery (the time from start of surgical intervention till its end), the extubation time (the time from discontinuation of isoflurane till removal of the endotracheal tube), the duration of anesthesia (time span from induction of general anesthesia till the extubation) and time for interaction (the time from discontinuation of isoflurane till verbal contact or response to commands) were recorded.

3. Statistical analysis

We assumed a clinically significant difference of 50% reduction in the requirements of additional hypotensive agent nitroglycerine to achieve the target MAP with a power of 80% and ($\alpha = 0.05$, one-tailed), and the sample size calculated was 36 patients (12/group) which will be increased to 45 patients (15/group) for possible dropouts. Microsoft Excel 2010 and Statistical Package of Social Science software program, version 21 (SPSS) were used for all statistical comparisons (Chicago, IL, USA). Continuous quantitative normally distributed data expressed as means and standard deviations (SD). Qualitative nominal data e.g. incidence of complications expressed as percentage. Fisher's exact test was used as appropriate to compare qualitative data between the study groups. All other group comparisons were made using analysis of variant (ANOVA) test and Kruskal–Wallis ANOVA was used to compare Ramsay sedation score and Fromme et al. field rating scale for bleeding between the three groups. P values of less than 0.05 were considered statistically significant.

4. Results

Forty-five adult patients, met our inclusion criteria, were enrolled in the study and randomly allocated into 3 groups, Dex-P (placebo), Dex-0.4 and Dex-0.8. All patients showed no significant differences regarding age, gender, weight, ASA classification, duration of surgery, duration of anesthesia and recovery characteristics including extubation time and time of interaction (Table 1).

The Fromme et al. bleeding score showed the lowest values in Dex-0.8 group and the highest values in group Dex-0.4. The differences between the three groups were statistically significant with ($P < 0.05$) at all assessment time points except at time 60 min, and there was no statistically significant difference between group Dex-P and Dex-0.4 (Table 2).

Among the three groups, the MAP showed no significant differences between the baseline values and values measured one minute after bolus dose, after induction of GA and after endotracheal intubation. The intraoperative MAP values in both group Dex-P and group Dex-0.8 were kept almost constant within target range of our study all through the time interval, while the intraoperative MAP within the group Dex-0.4 showed fluctuation to fall below the target range at some time intervals ($T_{20,\ 40,\ 60,\ 80}$) and above the target range at other time intervals ($T_{50,90)}$ (Fig. 1).

Table 1 Patients characteristics, duration of surgery, duration of anesthesia, extubation time and time of interaction in the three studied groups.

	Dex-P (n-15)	Dex-0.4 (n-15)	Dex-0.8 (n-15)
Age (years)	39 ± 7	33 ± 9	42 ± 3
Gender (male/female)	(9/6)	(7/8)	(5/10)
Weight (kg)	70 ± 9	68 ± 6	56 ± 11
ASA (I/II)	(11/4)	(13/2)	(10/5)
Duration of surgery (min)	118 ± 21	129 ± 18	112 ± 23
Duration of anesthesia (min)	135 ± 19	141 ± 20	148 ± 17
Extubation time (min)	15 ± 4	18 ± 5	21 ± 3
Time of interaction (min)	32 ± 8	35 ± 8	40 ± 5

Data expressed as mean ± (SD). *means P value < 0.05.

Table 2 Surgical field quality (Fromme et al. rating scale).

Time of assessment	Group Dex-P $n = 15$	Group Dex-0.4 $n = 15$	Group Dex-0.8 $n = 15$
30 min	2.4 ± 0.4*	3.5 ± 0.4*	1.4 ± 0.3*
60 min	2.2 ± 0.3	2.7 ± 0.5	1.2 ± 0.2*
90 min	2.1 ± 0.4*	3.8 ± 0.5*	1.3 ± 0.2*
End of surgery	1.8 ± 0.3	2.1 ± 0.2	0.9 ± 0.2

Data expressed as mean ± SD.
* Means P value < 0.05 among the three groups.

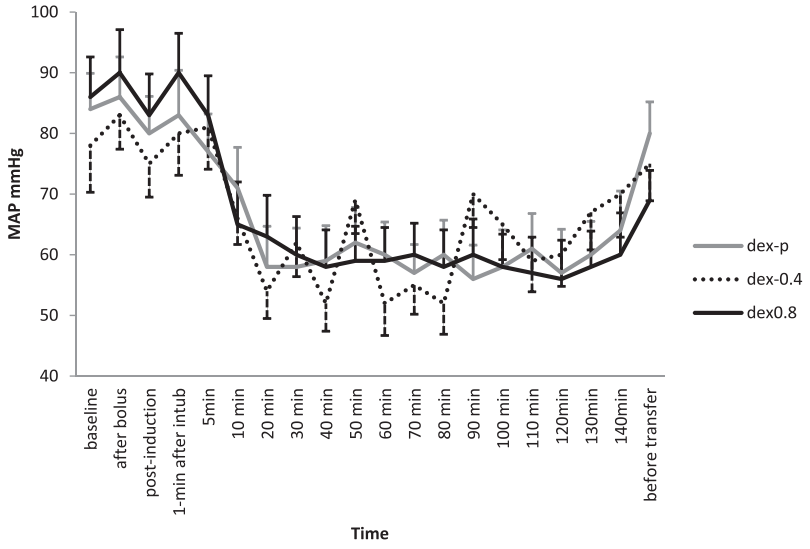

Figure 1 Intraoperative MAP in the 3 groups.

The baseline HR showed no significant difference between the three groups. One minute after the bolus dose of dexmedetomidine, the HR significantly decreased, about 25% from the base line values in the three groups ($P < 0.05$). HR rate did not significantly change after induction of GA in the three groups. One minute after tracheal intubation, HR increased in the three groups but this increase was not significant and did not reach the baseline values. In group Dex-0.8, the HR was significantly lower than that in Dex-0.4 and Dex-P from T_{20} till T_{120} ($P < 0.05$). HR showed no significant difference between group Dex-0.4 and group Dex-P except at $T_{30,80,130}$ the HR was significantly higher in group Dex-0.4 ($P < 0.05$) (Fig. 2).

The number of patients experienced hypotension with MAP < 55 mmHg and the number of ephedrine doses (one dose = 6 mg iv) required were significantly higher in group Dex-0.4 when compared to either Dex-P or Dex-0.8. The number of patients experienced bradycardia with HR < 50 beat/min and the number of atropine doses were comparable between the 3 groups (Table 3).

The target MAP was reached in all patients in group Dex-0.8 without need of using nitroglycerine infusion, unlike patients in group Dex-0.4 and Dex-p in which all patients needed nitroglycerine infusion to reach the target MAP. The requirements of nitroglycerine in group Dex-P were (10.8 ± 3.2 mg/patient) which was significantly higher than group Dex-0.4 (4.7 + 1.3 mg/patient) ($P < 0.05$) (Table 3).

Ramsay sedation scores measured in the PACU were significantly higher in both group Dex-0.8 and Dex 0.4 when compared to Dex-P at all time intervals. Ramsay score was higher in group Dex-0.8 when compared with group Dex-0.4 at all-time intervals ($P < 0.05$) (Fig. 3).

No significant difference between the three groups regarding the amount of atracurium besylate consumption, Modified Aldrete Score and adverse events as vomiting, laryngeal spasm or bronchospasm.

5. Discussion

In our study, applied on functional endoscopic sinus surgery in adult, dexmedetomidine as bolus dose 1 μg/kg iv followed by iv infusion of 0.8 μg/kg/h significantly decreased the MAP pressure to the target level without the need of an additional hypotensive agent nitroglycerin iv infusion and it provided the best surgical field quality by Fromme et al. rating score. And also dexmedetomidine as only bolus 1 μg/kg iv followed by nitroglycerine infusion decreased the MAP to the target level without significant increase in the HR and the surgical field conditions were satisfactory for surgeons. But dexmedetomidine as bolus dose 1 μg/kg iv followed by iv infusion of 0.4 μg/kg/h was not sufficient to lower the MAP to the target level and the use of an additional hypotensive agent nitroglycerin iv infusion was associated with fluctuation of the MAP above and below the target values and the surgical field conditions were not satisfactory for surgeons.

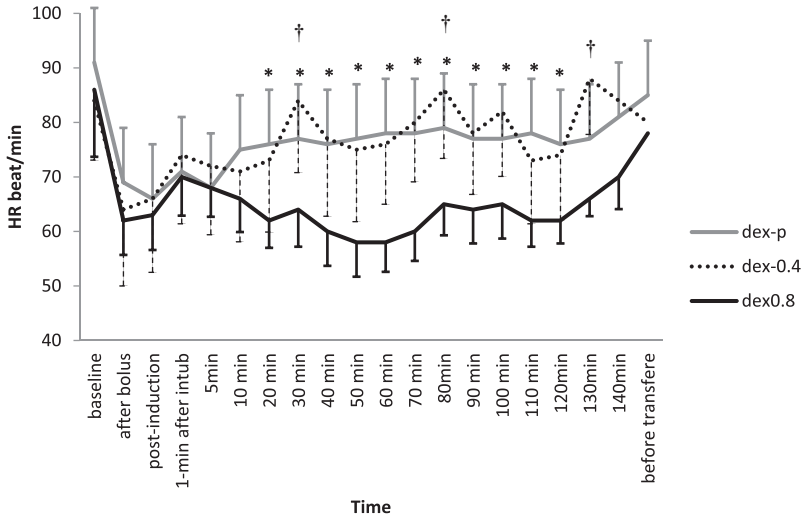

Figure 2 Intraoperative HR in the three groups: $^{*}P < 0.05$ in dex-0.8 vs dex0.4 & dex-p, $^{\dagger}P < 0.05$ in dex-p vs dex-0.4.

Table 3 Nitroglycerine, ephedrine and atropine requirement in the three groups.

	Dex-p	Dex-0.4	Dex-0.8
Total amount of nitroglycerin used/patient (mg)	10.8 ± 3.2*	4.7 ± 1.3*	0*
Ephedrine:			
Number & % of patients	3 (20%)†	9 (60%)†‡	2 (13.3%)‡
Number of doses/group			
	5†	21†‡	2‡
Atropine:			
Number and % of patients	0	2 (13.3%)	2 (13.3%)
Number of doses/group			
	0	2 (13.3%)	2 (13.3%)

Data expressed as (mean ± SD).
* *P*-value < 0.05 among the 3 groups.
† *P*-value < 0.05 (Dex 0.4 versus Dex-p).
‡ *P*-value < 0.05 (Dex-0.4 versus Dex-0.8).

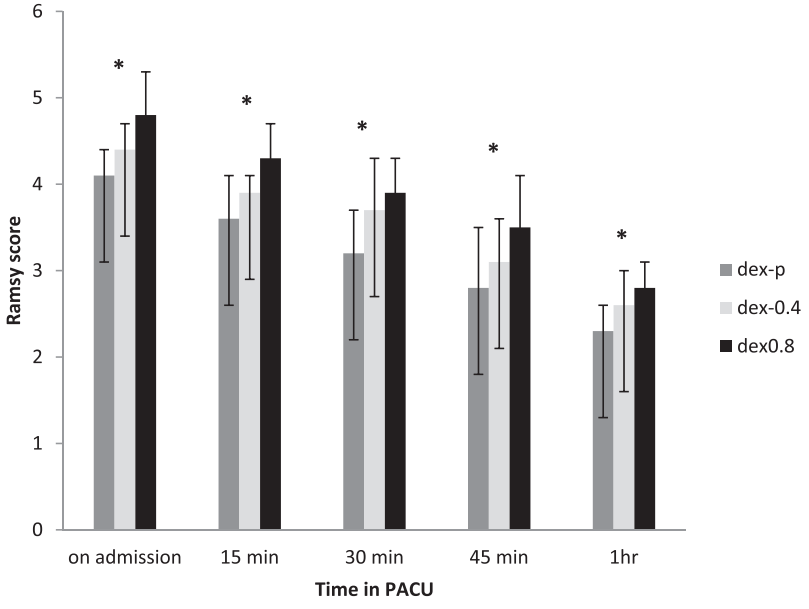

Figure 3 Ramsay sedation score: $^{*}P < 0.05$ among the three groups.

In our study, we chose a target MAP 55–65 mmHg to provide the best surgical conditions without the risk of tissue hypo-perfusion depending on a study conducted by Yoshikawa et al. [14] concluded that hypotensive anesthesia induced by using sodium nitroprusside or nitroglycerine in mandibular osteotomy to achieve MAP 60–70 mmHg is safe and associated with no significant increase in pyruvate, lactate or glucose levels, and another study conducted by Boezaart et al. [1] demonstrated that the best surgical conditions for FESS obtained when the MAP ranged between 50 and 54 mmHg. Also, it is reported that the best operative field quality in FESS surgeries by using Fromme et al. rating scale is 2–3 points [1,15]

Unfortunately, no sufficient clinical trials studied the effectiveness of combining α2-agonist (either clonidine or dexmedetomidine) infusion and direct vasodilator nitroglycerine infusing in producing controlled hypotensive anesthesia. In a study conducted by Sahin et al., comparing dexmedetomidine and alfentanil in producing hypotensive anesthesia during middle ear surgery, they had to use nitroglycerine iv infusion started from rate of 0.5 μg/kg/min in 3 out of 20 patients in dexmedetomidine group to achieve the target MAP 50–65 mmHg, however, they did not comment on the effect of such combination [24]. The synergistic effect of combining infusion of dexmedetomidine and nitroglycerin that found in our study group Dex-0.4 may be explained by the different mechanisms of action of both agents, the effect of premedication with α2-agonist on baroreflex response in anesthetized patients and the patient positioning required during FESS surgery.

Dexmedetomidine stimulates α2-receptors located in presynaptic nerve terminal enhances the negative feedback loop that inhibits the release of noradrenaline from the nerve terminal [16], while stimulation of the α2-receptor located in locus ceruleus of brainstem is responsible for the sedative and hypnotic effect of dexmedetomidine and its ability to reduce the central sympathetic output [16,17] both cause vasodilatation and decrease in blood pressure. It is should be noted that dexmedetomidine stimulates the postsynaptic α2-receptors in vascular smooth muscle and this produces vasoconstriction [16] which is opposed by endothelial nitric oxide synthesis [18].

Nitroglycerin has a non-specific, direct vasodilator effect on the venous capacitance vessels and incidentally on the arteries; it has a short half-life, it increases venous blood volume and reduces venous return, so cardiac output is proportionally reduced [2] Nitroglycerin mediates its action via its metabolite nitric oxide which activates guanylyl cyclase lead to increase cGMP, this will reduce the intracellular calcium and relax the vascular smooth muscle [16].

The baroreflex response is one of the body's homeostatic mechanisms for maintaining the blood pressure; it is mediated through the baroreceptors located in the aortic arch and carotid sinuses. The baroreflex response to increased blood pressure is mainly vagal (decreases the heart rate and blood pressure) while the baroreflex response to decreased blood pressure is mainly sympathetic (increases the heart rate and blood pressure) [19]. In a study conducted by Watanabe et al. [20], they demonstrated that in patients premedicated with α2-agonist clonidine and underwent general anesthesia, the baroreflex response to increased blood pressure is unchanged but become attenuated in response to decreased blood pressure.

The patient's position during FESS surgeries may play a role in explain the synergistic action of nitroglycerine and dexmedetomidine. Nitroglycerine especially in small dose causes vasodilatation more on the capacitance venous vessels rather than that on the arteriolar vessels, and with the patient's supine position with head up 30° commonly used in FESS surgeries, polling of the blood into the capacitance vessels helps in developing some degree of postural hypotension [21].

Referring to previous studies used dexmedetomidine to induce hypotensive anesthesia, In a placebo controlled clinical trial conducted by Ayoglu et al. [11], to assess to what extent the dexmedetomidine at infusion rate of 0.7 μg/kg/h is effective in reducing the bleeding from the surgical field during septoplasty and tympanoplasty. Despite authors could not achieve their target MAP (30% reduction from the preoperative value) at this infusion rate, but dexmedetomidine succeeded to provide a good surgical field.

Another clinical trial conducted by Aboushanab et al. [12], comparing the hypotensive effect of dexmedetomidine with that of magnesium sulfate during middle ear surgeries, they demonstrated that dexmedetomidine infusion at rate of 0.4–0.8 μg/kg/h succeeded to reduce the MAP to their target 60–70 mmHg, despite this MAP is higher than that used in our study but the authors demonstrated the ability of dexmedetomidine to provide very good surgical field.

Another placebo controlled trial conducted by Nasreen et al. [22], using low dose dexmedetomidine (0.4 μg/kg/h) in addition to titrated halothane vol% in order to reduce MAP 30% from the preoperative values during middle ear surgeries, they observed significant reduction in halothane requirement in dexmedetomidine group with better surgical field compared to placebo group.

Another observation in our study is the ability of the preinduction bolus dose 1 μg/kg of dexmedetomidine to attenuate the hemodynamic response to direct laryngoscopy and endotracheal intubation as no significant increase in HR or MAP in the 3 groups 1 min after inserting the endotracheal tube, the same observation was found in a study conducted by Bajwa et al. [23] whom reported the ability of dexmedetomidine 1 μg/kg iv infusion more than 20 min given as premedication to attenuate the pressor response to endotracheal intubation, surgery and extubation.

In our study, there was no significant difference in the extubation time or time of interaction between the three groups, a finding that can be explained by nature of dexmedetomidine as a sedative not hypnotic agent so patients receiving it will be sedated but easily arousable. Same observation found by Nasreen et al. [22] who reported significant reduction in the awakening time in patients receiving dexmedetomidine when compared to placebo group. But in disagreement with our finding, Aboushanab et al. [12] reported longer recovery time in patients receiving dexmedetomidine when compared to those received magnesium sulfate as hypotensive techniques during middle ear surgery. Also Richa et al [4] reported prolonged extubation time in patients receiving dexmedetomidine when compared to those received remifentanil for controlled hypotensive anesthesia during tympanoplasty.

Our study limitations include the following: first inability to assess the depth of anesthesia and the effect of dexmedetomidine on isoflurane requirements due to unavailability of BIS monitoring. Second we did not use a score for assessing the postoperative pain, however the FESS is usually followed headache sensation rather than pain and it was managed

successfully by iv paracetamol preparation on patients complained.

6. Conclusion

From our clinical trial applied on functional endoscopic sinus surgery in adult ASA I,II we concluded that, dexmedetomidine regimen as pre-induction bolus dose 1 μg/kg iv followed by post-induction continuo iv infusion 0.8 μg/kg/h significantly decreased the mean arterial blood pressure to the target level without the need of an additional hypotensive agent nitroglycerin, and it provides the excellent surgical field quality when compared to other regimens.

Dexmedetomidine used as only pre-induction bolus dose 1 μg/kg iv followed by post-induction nitroglycerine iv infusion decreased the mean arterial blood pressure to the target level and avoid the reflex tachycardia and provide satisfactory surgical field quality.

Conflict of interest

No conflict of interest in this study.

Appendix A. Ramsay sedation score

Score	Observation
1	Anxious, agitated or restless
2	Cooperative, oriented and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory Stimulus
6	Asleep, no response

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